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Review

Common variable immunodeficiency and autoimmunity – an inconvenient truth☆

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ABSTRACT

Coexisting morbidities in CVID include bronchiectasis, autoimmunity and malignancies. The incidence of autoimmune disease in CVID patients may approach 20% of cases. The most common autoimmune disease found in CVID patients is autoimmune cytopenia, but rheumatoid arthritis, lupus, and now primary biliary cirrhosis have also been reported. The coexistence of immunodeficiency and autoimmunity appears paradoxical, since one represents a hypoimmune state and the other a hyperimmune state. However, this paradox may not actually be all that implausible due to the complex nature of immune cells, signaling pathways and their interactions. The cellular alterations in combined variable immunodeficiency include a range of T and B cell abnormalities. Selective immune derangements found in CVID include a downregulation of regulatory T cells (Treg cells), accelerated T cell apoptosis, abnormal cytokine production secondary to cytokine gene polymorphisms and increased autoreactive B cell production. The impact of these abnormalities on T and B cell interaction may not only explain the immunodeficiency but also the development of autoimmunity in select groups of patients with CVID. The variability in the clinical manifestations of CVID as a result of this immune interaction suggests that CVID is not one disease but many. This is important because it follows that the treatment of CVID may not always be the same, but may need to be directed specifically towards each individual patient.

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Abbreviations: ADAM, a disintegrin and metalloproteinase; AHA, autoimmune hemolytic anemia; AID, activation induced cytidine deaminase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; BAFF-R, B cell activating factor of the tumor necrosis factor family receptor; CT, computed tomography; CVID, combined variable immunodeficiency; EBV, Epstein-Barr virus; G-CSF, granulocyte colony stimulating factor; GWAS, genome wide association study; ICOS, inducible costimulator; ITP, idiopathic thrombocytopenic purpura; IVIg, intravenous immunoglobulin; JIA, juvenile idiopathic arthritis; NK, natural killer; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis; RESPI, recurrent sinpulmonary infections; RTE, recent thymic emigrants; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphisms; TACI, transmembrane activator and calcium – modulator and cyclophilin ligand interactor; Tfh, T follicular helper; THI, transient hypogammaglobulinemia of infancy; TNF, tumor necrosis factor.

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1. Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency (PID) in adults. It is characterized by a widely varying clinical spectrum. Most common clinical manifestations include varying degrees or severity of hypogammaglobulinemia, recurrent infections, autoimmune diseases, lymphoid malignancy, enteropathy and granulomatous diseases.

The onset of symptoms related to CVID may begin to appear in childhood, but more commonly, the disease presents in its full form in the second or third decade of life. However, it does seem to present earlier in males than in females [1]. According to a longitudinal study conducted over four decades and published in 2012, the survival of CVID patients is lower than that of normal controls, but the contributions to mortality from various complications differs widely. It is noteworthy that noninfectious complications, such as lymphoma, hepatitis, lung impairment, and enteropathy, are important risk factors of death in CVID patients [2]. However, not all comorbidities (e.g. lymphoma, autoimmune diseases) cause the same reduction in life expectancy [2]. The development of antibiotics and the common application of immunoglobulin replacement therapy have significantly reduced the incidence of severe infections and increased the survival rate in recent years.

1.1. CVID and autoimmunity

The association of CVID and autoimmunity is well recognized [3]. Teleologically, one may think that this association is impossible. Why would someone with an immune deficiency also present with diseases that are consistent with a hyperactive immune system? The fact that this is indeed the case illustrates the complexity of the immune system [4–7]. In fact, the association of immunodeficiency with autoimmunity has been reported with many other immunodeficiency states including selective IgA deficiency [8]. The key to understanding this relationship is to realize that the immune system is in constant balance and counterbalance, with stimulatory and inhibitory factors that affect common cells, driving certain aspects of pathways that can lead to autoimmunity on one hand, and immunodeficiency on the other. This discussion includes genetic, epigenetic and environmental interactions [9–12].

Once one understands this, then it is not at all unexpected that CVID patients have accompanying autoimmune or inflammatory diseases. Malignancies such as non-Hodgkins lymphoma have also been associated with CVID. Autoantibodies and auto-reactive B cells can in fact be detected in patients whose total serum immunoglobulins are very low and specific response to antigens is severely impaired. According to studies from United States and Europe, autoimmune diseases occur in approximately 20–30% of patients with CVID, with a slight female predominance [2,13–15]. In this paper, a CVID patient who also developed primary biliary cirrhosis (PBC) is described and the relevant medical literature is reviewed to summarize the mechanism and treatment of CVID and autoimmunity.

1.2. Epidemiology of CVID

In the European Society for Immunodeficiencies Database, data on 2212 CVID patients from 28 medical centers were analyzed. In this group, early disease onset was quite common (33.7% diagnosed in age younger than 10 years). The incidence of CVID is estimated to be between 1:25,000 to 1:50,000 in Caucasians. It appears to be equally prevalent in males and females, but less common in Asians and African-Americans [2]. CVID is the most common symptomatic primary immunodeficiency disorder. The total number of patients in the registry from a total of 30 countries as of 2014 (data collection began in 2004) is 18,700. Thus CVID accounts for 11.8% of all immunodeficiency patients in this registry. Other countries and regions have established registries as well, including the European CVID registry, the French DEFI group and the Italian Primary Immunodeficiencies network (IPINET). In the United States, the US Immunodeficiency Network (USIDNET) enrollment through 2012 includes 853 patients with CVID out of a total of 3025 registered immunodeficiency patients, accounting for 28.2% of patients.

2. Case Report

2.1. History

A 28-year-old Chinese male was transferred to Renji hospital, Shanghai, China, with a history of high fever, classical measles rash and Koplik' s spots which developed after measles vaccination. In addition, jaundice and pneumonia developed over the past month. Complete blood count was consistent with pancytopenia (Table 1). Liver function test showed significantly increased total bilirubin. Alanine aminotransferase (ALT), serum aspartate aminotransferase (AST) and alkaline phosphatase levels were also elevated. He was found to have severe hypogammaglobulinemia, with serum immunoglobulin(Ig)G, IgA and IgM concentrations reported to be 2.73 g/L(reference range 8 to 16), 0.23 g/L (reference range 0.7–3.3) and 0.17 g/L (reference range 0.5–2.2) respectively.

Screening for antoimmune diseases revealed that the patient was positive for antinuclear antibody (ANA, titer 1:100), antimitochondria antibody (AMA, titer 1:100), anti-AMA-M2 and anti-M2-3E antibody (by indirect immunofluorescent assay, Euroimmun, Lubeck, Germany). Tests for antibodies to smooth muscle, double stranded DNA, liver-kidney microsome, sp100, gp210 and neutrophil cytoplasm were negative. There was no evidence of infection with hepatitis viruses A, B, C, cytomegalovirus, Epstein-Barr virus or human immunodeficiency virus. Wilson's disease and hemochromatosis were excluded by testing for ceruloplasmin and ferritin levels. He denied a history of alcohol or drug abuse, and had no family history of liver or immunodeficiency disease. Ultrasound and Computed tomography (CT) scan of the abdomen showed hepatosplenomegaly. Chest CT scan showed a focal infiltrate in the middle lobe of the right lung.

Table 1
Laboratory tests of patient with CVID and PBC.

Lab values	Patient's value	Reference range
Complete blood count		
White blood cell count (10^9/L)	2.3	3.97-9.15
Neutrophils (10^9/L)	1.4	2.0-7.0
Lymphocytes (10^9/L)	0.6	0.8-4.0
Monocytes (10^9/L)	0.2	0.12-1.0
Hemoglobin (g/dl)	111	131-172
Platelet (10^9/L)	78	85-303
Liver function tests		
ALT (U/L)	156	0-40
AST (U/L)	137	0-40
Alkaline phosphatase (U/L)	255	40-150
Total bilirubin (μmol/L)	194	0-21
Direct bilirubin (μmol/L)	150	0-5
Immunoglobulins		
Ig G (g/L)	2.73	8-16
Ig A (g/L)	0.23	0.7-3.3
Ig M (g/L)	0.17	0.5-2.2
Flow cytometry analysis		
CD3+ Cells (% of lymphocytes)	78.6	66 ± 10
CD4+ Cells (% of lymphocytes)	45.5	44 ± 9
CD8+ Cells (% of lymphocytes)	33.1	31 ± 7
CD16 + 56+ Cells (%of lymphocytes)	9.8	15 ± 6
CD20+ cells (% of lymphocytes)	9.5	11 ± 4
CD20 + 27 + cells (% of CD20 + cell)	6.16	31.4 ± 9.2
CD20 + 27 + 43+ cells (% of CD20 + CD27 + cell)	8.9	7.9 ± 2.4
CD20 + 27 + 43+ Cells (% of CD20 + cell)	0.55	2.5 ± 0.8

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

A further flow cytometric analysis was conducted to establish peripheral B cell, T cell and NK cell counts. All were within normal limits except for a slightly increased CD3+ cell population. Putative B1 cells, identified as $CD20^+CD27^+CD43^+$ cells, in healthy controls and in the CVID patient were measured according to the reported flow cytometric assay [16]. The percentage of $CD20^+CD27^+$ cells was greatly diminished in the patient, however, the percentage of B1 cells in $CD20^+$ cells was in the normal range when the deficiency of $CD20^+CD27^+$ cells was taken into account, which is consistent with the B lymphocyte patterns reported from other studies [16].

Ursodeoxycholic acid and monthly intravenous immunoglobulin (IVIG) (400 mg/kg once per month) were administered. Fever, rash and pneumonia were resolved but liver function progressed to liver failure after 6 months from the time of diagnosis. A liver transplantation was performed and the resected liver tissue was examined for histopathological changes (Fig. 1). Liver resection specimens showed cirrhosis and regenerative nodules. Numerous inflammatory cells were found to have infiltrated the portal tract. The presence of ductopenia and ductular proliferation were detected by immunohistochemical staining of CK7. The patient was given tacrolimus to prevent liver rejection after the operation. Liver function improved during the subsequent 1 month follow-up period.

2.2. Case analysis

CVID was first described about 60 years ago, and is characterized by low immunoglobulin levels and a failure to respond to protein or polysaccharide antigens. However, over the years CVID has often become a clinical "waste basket" for immunodeficiencies that are not otherwise able to be characterized. The current consensus is that a diagnosis of CVID requires immunoglobulin levels that are at least 2 standard deviation below the mean for age in serum IgG and IgA and fulfills all of the following criteria: 1) onset of immunodeficiency at greater than 2 years of age; 2) absent isohemagglutinins and/or poor response to vaccines; and 3) exclusion of other defined causes of hypogammaglobulinemia [17]. There is some variability on the required age criteria, as some sources, rather than age of onset, would use an age of 4 years with persistently low immunoglobulin levels as a criteria for diagnosing CVID, due to the possibility of transient hypogammaglobulinemia of infancy (THI). With the knowledge of the genetic basis in some cases of CVID, coupled

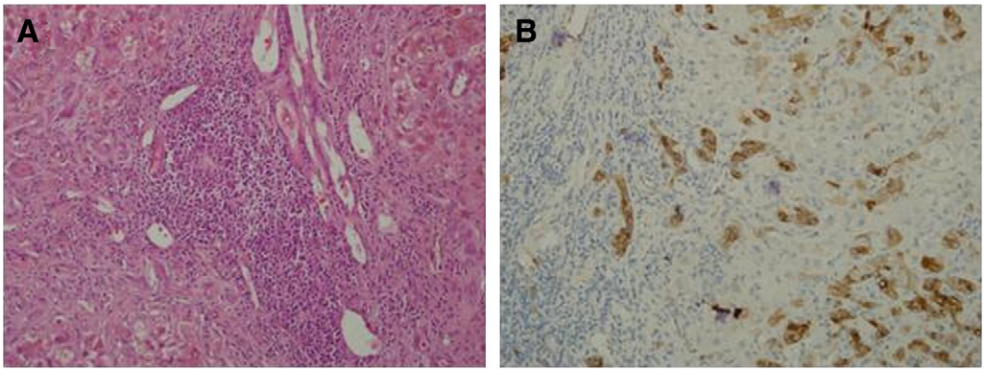

Fig. 1. Pathological findings of the liver resection specimen. A: Hematoxylin and eosin staining shows portal tracts with numerous inflammatory cell infiltration (200×). B: CK7 immunohistochemical staining shows ductopenia in portal tracts and ductular proliferation in periportal regions (200×).

with an increased understanding of the mechanisms of the disease, these criteria are continually redefined [18]. Nevertheless, based on current accepted diagnostic criteria, the patient described in this article satisfies the diagnosis of CVID.

In addition, our patient was also diagnosed with primary biliary cirrhosis (PBC). PBC is an autoimmune liver disease, predominantly affecting middle aged-women. The diagnosis of PBC requires the presence of two of the following three features: 1) elevation of liver enzymes for more than six months; 2) histological evidence of portal tract inflammation; 3) a positive AMA [19]. The patient in this article satisfied all of these diagnostic criteria. Other autoimmune diseases, including idiopathic thrombocytopenia purpura (ITP), autoimmune hemolytic anemia (AHA) and rheumatoid arthritis, were ruled out by relevant tests and physical examination.

Although three cases of co-existing CVID and PBC have been previously reported [14], this is the first case described in China. With periodic IVIG infusions, the level of IgG in this patient was maintained between 340–540 mg/dl, and no infections occurred during the period when he was receiving infusions. To date, a desired or optimal trough level has not been defined in CVID patients. The determination of the correct trough level depends upon the clinical history and severity and frequency of infections, and is thus different for each patient. The attainment of individual IgG trough levels must meet the clinicians' goal of controlling infections. Despite aggressive treatment with ursodeoxycholic acid, the patient's liver disease still deteriorate rapidly. After the liver transplantation, the patient was given tacrolimus to prevent liver rejection. Liver function of the patient was significantly improved after the operation. Although the immunologic indices of the patient were still abnormal, no severe infection occurred after the treatment of tacrolimus, suggesting a safe application of tacrolimus treatment in this liver transplant patient with CVID.

3. Literature review

3.1. CVID associated autoimmune disease – clinical correlates

3.1.1. Hematologic diseases

Although there is variation in the prevalence of autoimmune diseases from different studies, the most common autoimmune conditions associated with CVID are hematologic cytopenias, which may be present in up to 25% of CVID patients with some form of autoimmunity [20]. The breakdown includes idiopathic thrombocytopenia purpura (ITP), present in up to 7% of CVID patients, autoimmune hemolytic anemia (AHA), present in up to 4%, and autoimmune neutropenia, occurring in about 1% of CVID patients. It should be noted that these are typical rates found in 1 study and that there is considerable variability when multiple studies are considered. The combination of AHA and ITP (Evans' syndrome) has also been reported in patients with CVID [2,13–15].

Replacement of IgG immunoglobulin with intravenous Immunoglobulin (IVIg) significantly reduces the incidence of pneumonia in CVID patients. In addition, IVIg appears to reduce the frequency of recurrent ITP and AHA as well, indicating the possibility for one agent that can treat immunodeficiency and autoimmunity simultaneously [21]. In contrast, another study concluded that ITP does not respond to IVIg replacement therapy [22].

Other modes of therapy include corticosteroids, as well as immunosuppressive agents such as azathioprine and cyclophosphamide. Corticosteroids are often first option for treating the autoimmune and inflammatory conditions. Alternative treatments are available for patients who have failed steroid therapy, or who experience significant side effects from the use of chronic steroids. Splenectomy has also been reported to be effective in the treatment of ITP and AHA, but this strategy must be approached with care because of the risk of infection by encapsulated bacterial in CVID patients [23]. Other drugs, such as azathioprine, danazol, cyclophosphamide, vincristine, rituximab, recombinant granulocyte colony stimulating factor (G-CSF) have also been used in individual CVID cases with hematologic complications [13,22]. While immunosuppressor treatment often proves to be helpful, the accompanying increased risk of severe infections must be taken into consideration [21,24].

3.1.2. Rheumatologic diseases

Rheumatoid arthritis (RA) or juvenile rheumatoid arthritis (JIA) occurs in 1–10% of CVID patients [25]. Multiple joints (the knees, ankles, and hands) may be affected, leading to joint destruction. Antinuclear antibodies and rheumatoid factors are typically absent in CVID. While typically not seen in RA in non-CVID patients, CVID patients may have synovial hyperplasia and capillary proliferation without major lymphocytic or polymorphonuclear infiltrate. Systemic lupus erythematosus (SLE) appears to be uncommon in CVID. About 90% patients with both CVID and SLE are females [26].

The treatment for CVID associated rheumatologic disease is the same as for the primary autoimmune condition, along with appropriate immunoglobulin replacement [27]. Hydroxychloroquine has been proven to be safe and effective in the treatment of rheumatologic diseases in CVID. Other immunomodulators, such as cyclophosphamide, azathioprine, and mycophenolatemofetil, may reduce serum Ig, which can add a level of complexity to the diagnosis of CVID [28].

3.1.3. Gastrointestinal diseases

Inflammatory bowel–like disease has been described in 6–10% of patients with CVID. Histologic patterns in CVID biopsies often mimic diseases such as graft-versus-host disease, lymphoid hyperplasia, and villous atrophy resembling celiac sprue [29]. Liver diseases including primary biliary cirrhosis and autoimmune hepatitis, have also been observed in patients with CVID, with persistently elevated liver enzymes detected. Pernicious anemia is another autoimmune disease noted in a small percentage (1–9%) of patients with CVID [15].

Intestinal inflammation in CVID is difficult to treat. Antibiotics are often prescribed. Prolonged oral steroid treatment is not ideal given the risk of immunosuppression, although it is likely to reduce symptoms. Locally acting corticosteroids, immunomodulators (6-mercaptopurine or azathioprine), and tumor necrosis factor (TNF) inhibitors (eg, infliximab) have also been used in select cases.

3.1.4. Dermatological diseases

Dermatological conditions have been occasionally reported in CVID, including alopecia totalis, vitiligo, and psoriasis [30]. In rare cases, Sweet's syndrome (SS) and pyoderma gangrenosum have also been reported [31,32]. Intravenous immunoglobulin replacement therapy and oral broad spectrum antibiotic therapy have been shown to be effective in the treatment of these diseases in CVID patients.

4. Mechanism of CVID-associated autoimmunity

Although the mechanism of CVID-associated autoimmunity remains elusive, both genetic and cellular mechanisms have been hypothesized to play a role in pathogenesis. However, CVID is a heterogeneous group of diseases, and it is likely that the genetic defect is polygenic rather than monogenic. A genome wide association study (GWAS) evaluated 363 patients with CVID for single nucleotide polymorphisms (SNPs) in 610,000 genes. The authors found a strong association with a disintegrin and metalloproteinase (ADAM) gene regions as well as major histocompatibility complex (MHC) regions. Their data suggests that the limited number of genes that have so far been attributed to occur in CVID is but the tip of the iceberg [33,34].

4.1. Genetic factors in CVID

Although most cases of CVID are sporadic, there is a family history in about 20–25% of cases, which indicates a role for genetics in the

pathogenesis of this subset of patients with CVID. It is now known that CVID, despite the current diagnostic guidelines, is likely not one, but many different diseases [35]. Several genetic defects have been described among CVID patients in recent years, and the genes involved include inducible costimulator (ICOS), transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), B-cell activating factor of the tumor necrosis factor family receptor (BAFF-R), CD19, CD20, CD21, or CD81 [36,37]. Mutations in these genes affect the expression of these factors, all of which are involved in the immune response. The effects that these genes have on signaling pathways may be diverse, and contribute not only to immunodeficiency diseases, but also autoimmune disease. For example, ICOS is expressed on T cells and exerts an important effect on the terminal differentiation of B cells into memory cells. Therefore, defective ICOS expression might lead to B cell dysregulation, leading to the development of autoimmunity states.

Schroeder et al. analyzed TCI mutations in CVID and patients with a history of recurrent sinopulmonary infections (RESPI) and found that CVID patients have mostly inherited HLA *DQ2, *DR7, *DR3(I7), *B8 and/or *B44 [38]. In a subsequent study, Waldrep et al. also analyzed for mutations in TACI, and found that 11 of the 76 total patients tested heterozygous for the silent T- > G polymorphism at proline 97 in exon 3 (rs35062843). However, since only one of their patients inherited a TACI allele that was previously reported to be associated with CVID, the authors suggest that in CVID patients in whom a previously recognized MHC allele has been identified, TACI mutations are less likely to play a significant role in pathogenesis [39].

On the other hand, a mutation in the *TNFRSF13B* gene, which encodes TACI, is found in 7–10% of patients with CVID. A study of CVID patients who carry one or two TACI mutations showed that autoimmunity is closely related to having only one TACI mutations. These patients were found to have circulating T follicular helper (Tfh) cells and an increased incidence of anti-nuclear antibody positivity. Tfh cells likely play a role in the development of autoreactive B cells. In CVID patients with autoimmunity, TACI mutations are thought to interfere with the development of B cell tolerance. In this study, the investigators found that TACI mutations affected the ability for the individual to experience normal function at the central B cell tolerance checkpoint, which affected the ability of the subjects to remove autoreactive B cells. This is believed to be mediated by the ability of TACI to impose B cell receptor and Toll-like receptor defects. In healthy individuals, this lack of development of B cell tolerance centrally will be caught at the peripheral B cell tolerance checkpoint, which is independent of TACI. However, in patients with CVID, peripheral tolerance is also defective and this leads to persistent of autoreactive B cells and autoimmune disease [40]. Interestingly, patients with two TACI mutations appeared to be protected against the development of autoimmune diseases.

4.2. Cellular mechanisms

4.2.1. B cell autoreactivity

The breakdown of self-tolerance and enhanced auto-reactivity in CVID may be caused by loss of the homeostatic immunologic regulatory network for B cells [36]. Whether or not the mechanisms involved in primary autoimmune diseases such as systemic lupus erythematosus are the same as those in play in CVID associated autoimmunity is unclear [41]. For example, it is now clear that there is a role of T cell apoptosis in SLE, but is this a mechanism that also plays a role in CVID patients who develop SLE? [42]

A reported characteristic of CVID has been a failure in B cell differentiation [43] and class switch recombination [44]. The low level of mature B cells in peripheral circulation implies a reduction in the production of immunoglobulins [45]. This would lead one to infer that CVID patients with autoimmunity may have distinctive characteristics as compared to those without autoimmunity, such as a deficiency of isotype switched memory B cells.

Warnatz et al. [46] demonstrated that patients who have reduced numbers of switched memory B cells and an increased proportion of CD21 − peripheral B cells have increased frequency of splenomegaly and autoimmunity. From the French DEFI registry, a large European study of 311 patients with CVID revealed 55 patients with autoimmune cytopenia and 61 patients with clinical or serologic evidence of other autoimmune diseases. The study also found that there was an increased percentage of $CD21^{low}$ B cells in CVID associated autoimmune cytopenia. Accompanying this finding was a higher expression of CD95 and HLA-DR on activated T cells, and a decrease number of naïve T cells [47]. This finding was not seen in other autoimmune disease in CVID patients, although a separate study showed an increase in proportion of $CD21^{low}$ B cells in patients with CVID and rheumatoid arthritis [48]. These two studies suggest that the development of autoimmunity in CVID patients requires both a restricted subset of B cells and also T cell help. A study of 52 patients with CVID, of whom 14 had at least one autoimmune manifestation during the study period, it was found that those with autoimmune disease had increased serum IgM levels and a reduction in switched memory B-cells [49].

The profound immune dysregulation in CVID patients may also cause expansion of autoimmune B cell clones or allow them to escape normal regulatory controls due to defective receptor editing. Enhanced abnormal somatic hypermutation in B cells has also been reported [50]. In addition, defective antigen clearance may result in end-organ deposition of complexes, leading to inflammation and perhaps the formation of anti-tissue antibodies.

A study of TACI mutations in families of patients with CVID revealed that intra- and extracellular expression of TACI in B cells was defective when there was a TACI mutation detected. The study also revealed that TLR9 did not upregulate B cell TACI expression in patients and family members, as it normally does. Hypogammaglobulinemia was only found in patients with CVID, but not in healthy relatives. The effect of activation of TACI on B cells is to induce isotype switching, through the expression of activation induced cytidine deaminase (AID). In patients with TACI mutations and reduced TACI expression, the expression of AID mRNA was impaired in B cells of Epstein-Barr Virus (EBV) cell lines from patients with CVID [51].

4.2.2. The role of T cells in CVID associated autoimmunity

Although the pathologic mechanism of CVID appears to be related to defects in immunoglobulin-producing B cells, T cell defects have been also described in subgroups of T cells, such as reduced T-regulatory cells, reduced CD4 and increased $CD8^+$ T cells [52–54].

The numbers of naïve T cells were evaluated in CVID patients in a study by Oraei et al. in 2012. Naïve T cells, $CD45RA^+CD62L^+CD4^+$ T cells were lower in male compared to female patients and also when compared to normal male controls. Recent thymic emigrants (RTE) cells were also lower in this group. There was no difference between normal male and female controls. When the patients were divided according to the percentage of naïve T cells (Group 1 ≤33% naïve T cells, and Group 2 >33% naïve T cells), the authors found that there was a higher incidence of autoimmunity in Group 1. The percentage of RTE cells was also lower in the autoimmunity group than those without autoimmune manifestations of their CVID [55]. This study suggests that the pathogenesis of autoimmunity in CVID patients may involve a defect in thymic output of $CD4^+$ T cells.

Carter et al. [56] found a reduced level of regulatory T cells (Treg cells) in CVID patients with autoimmunity. He also demonstrated that patients with autoimmunity had a reduced expression of CD25 and CTLA-4. The level of T cell activation markers was the same as that in CVID patients without autoimmunity. This study was limited by the small number of patients [56]. However, other studies have demonstrated similar findings [57,58]. Genre investigated 33 subjects with CVID and found that compared to age and sex matched controls, the CVID patients demonstrated a reduced frequency of $CD4^+CD25^{hi}FoxP3^+$ cells with diminished FoxP3 expression. Of these patients, 1/3 or 11 patients had some form of

autoimmune disease. In addition to the reduced expression in CVID patients compared to controls, the authors found a further decrease in FoxP3 expression in those patients with autoimmune disease when compared to those without (46 ± 5.77 vs. 67.05 ± 6.18) [52].

It has been postulated that the reduced number of Treg cells may be driven by a defect in B cell homeostasis, in which an elevated number of regulatory B cells expressing $CD19^{+}CD24^{hi}CD38^{hi}$ were found in CVID patients with autoimmunity, reflected an expanded regulatory B cell pool with reduced IL-10 production. In addition, the numbers of switched memory B cells, $CD19^{+}CD27^{+}IgD^{-}$ were reduced in the group with autoimmunity, though not exclusively [59].

4.2.3. Other cellular abnormalities that may contribute to autoimmunity in CVID patients

Impaired differentiation, maturation, and function of dendritic cells was also reported to be involved in the pathology of CVID and autoimmunity [60]. Abnormality of various cytokines, including decreased IL-2, IL-4, IL-6, IL-7, IL-10, interferon-γ production and excess TNF, BAFF, APRIL production in a subset of patients, have also been reported [61]. Park et al. reported that there is a chronic upregulation of interferon responsive genes in CVID patients with autoimmune diseases and other inflammatory comorbidities compared with patients with uncomplicated CVID, XLA patients or normal controls [62]. The authors suggest that it is the impairment in adaptive immunity that leads to chronic activation of innate immune pathways such as interferon signaling pathways in response to environmental stimuli [62].

It remains unclear whether these abnormalities are primary events or secondary downstream abnormalities [36]. Soluble CD26 and CD30 levels are increased in patients with CVID indicating a skewing of immune response towards a Th1 phenotype. However, there is no difference in soluble CD30 levels in CVID patients with and without autoimmunity [63].

5. Conclusion

Autoimmune manifestations are frequent in patients with CVID. The diagnosis of CVID and autoimmunity should be made promptly since it may influence the therapeutic strategy. The pathogenesis of CVID associated autoimmunity remains obscure and further research is needed to clarify the genetic and cellular mechanisms. The finding of a high incidence of $CD21^{low}$ B cells is significant as these cells have been found to be enriched for autoreactive germline antibodies. The finding of a lower number of naïve T cells and RTE T cells in CVID patients with autoimmunity versus those without indicates a role of thymic output in the pathogenesis of autoimmunity in CVID patients. These observations suggest that the coexistence of autoimmunity and immunodeficiency is a result of dysfunction in multiple related immune pathways or factors (Table 2) [20].

It should also not be forgotten that even in patients without an immunodeficiency, infections and autoimmune disease are often closely related [64]. This may take the form of infectious agents as causative factors of autoimmune diseases, or the observation of higher susceptibility to infections in patients with autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus. The mechanisms behind these inter-relationships may cross paths with the same mechanisms that may drive the increase of autoimmune diseases in CVID [65].

Table 2
Potential mechanisms for autoimmunity in CVID patients.

Increased in autoreactive B cells
Reduction in activity of B regulatory cells
Accelerated T-cell apoptosis
Primary T cell abnormalities
Reduced generation of antigen-specific memory T cells
Abnormal cytokine production

As we learn more about the genetic predisposition the relationship between genetic mutations and immune function in CVID, we may become more able to decipher the complex mechanistic pathways that lead to the development of autoimmunity. Moreover, with a better understanding, we may also be able to develop efficient biomarkers for diagnosis and effective treatment, as well as being able to predict which patients with CVID may be more prone to developing autoimmune diseases.

Take-home messages

- Autoimmune disease is a common manifestation of combined variable immunodeficiency.
- The co-existence of hypo- and hyper-immune states in the same individual at the same point in time is not implausible given the complexity of the immune system.
- Both T and B cells abnormalities may contribute to the development of autoimmunity in CVID patients.
- Increased autoreactive B cells and reduced T regulatory cells may be involved in the pathogenesis of autoimmunity in CVID.
- The genetic influence on CVID is like polygenic, contributing to the heterogeneity of the disease and the variability in the incidence of autoimmunity and other comorbidities.

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